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Supplementary appendix 3

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Methods: Statistical Analysis

To evaluate risk factors associated with the daily probability of being delirious in the ICU in COVID-19 patients, we used a first-order Markov multinomial model incorporating competing risks. Our outcome, daily mental status is nominal in nature. Daily mental status is a variable that consists of five levels: delirious, comatose, normal, death and discharge. Since there is not a natural ordering to these levels, the recommended and most commonly used statistical model to accommodate this is the multinomial logistic regression model. A patient can be in the ICU for multiple days and hence this data is longitudinal in nature as well. This longitudinal unordered outcome modelled using the following multinomial logistic regression model is formulated as below:

$$\ln \left(\frac{P(\text{mental status}_{ij} = \text{delirious})}{P(\text{mental status}_{ij} = \text{normal})} \right) \\ = b_{10} + b_{11}(\text{previous day mental status}) + b_{1p}(\text{covariates})$$

where $\text{mental status}_{ij}$ is the mental status response for subject i on the jth day. Here the probability distribution of the response is multinomial, and this model reduces to a logistic regression model in the special case if there are only two mental states. Here the coefficients b represent effects on the log-odds of membership in level k versus the reference level of the response.

Although we are interested primarily in the probability of being delirious, the other levels are competing events and need to be considered to obtain accurate estimates and to be consistent with the states that a patient goes through while in the ICU. Given the fluctuating nature of delirium over the course of a patient's ICU stay, along with baseline and daily risk factors for its occurrence; it is important to use a competing risk Markov model with time-dependent methods when evaluating the risk of delirium. The multinomial model provides an alternative approach to estimating a competing risks model and provides explicitly for competing risks by treating the dependent variable as a polytomous variable. The time-dependent factor is incorporated by including the previous day's mental status as a covariate in the model, which is also often referred to as a first-order Markov model. Although higher-order Markov models (where the current mental status depends on two or more preceding ones) could always be entertained, the transition probability matrix ends up being unwieldy, clinically not interpretable and the degrees of freedom needed to accommodate those transitions also remain a limitation. Robust variance estimates were also used to account for correlation beyond the first-order Markov assumption.

Table S1: COVID-19 Intensive Care International Study Group study sites and investigators

Country	City	Site Name	Lead Investigator/Collaborator	Additional Collaborators
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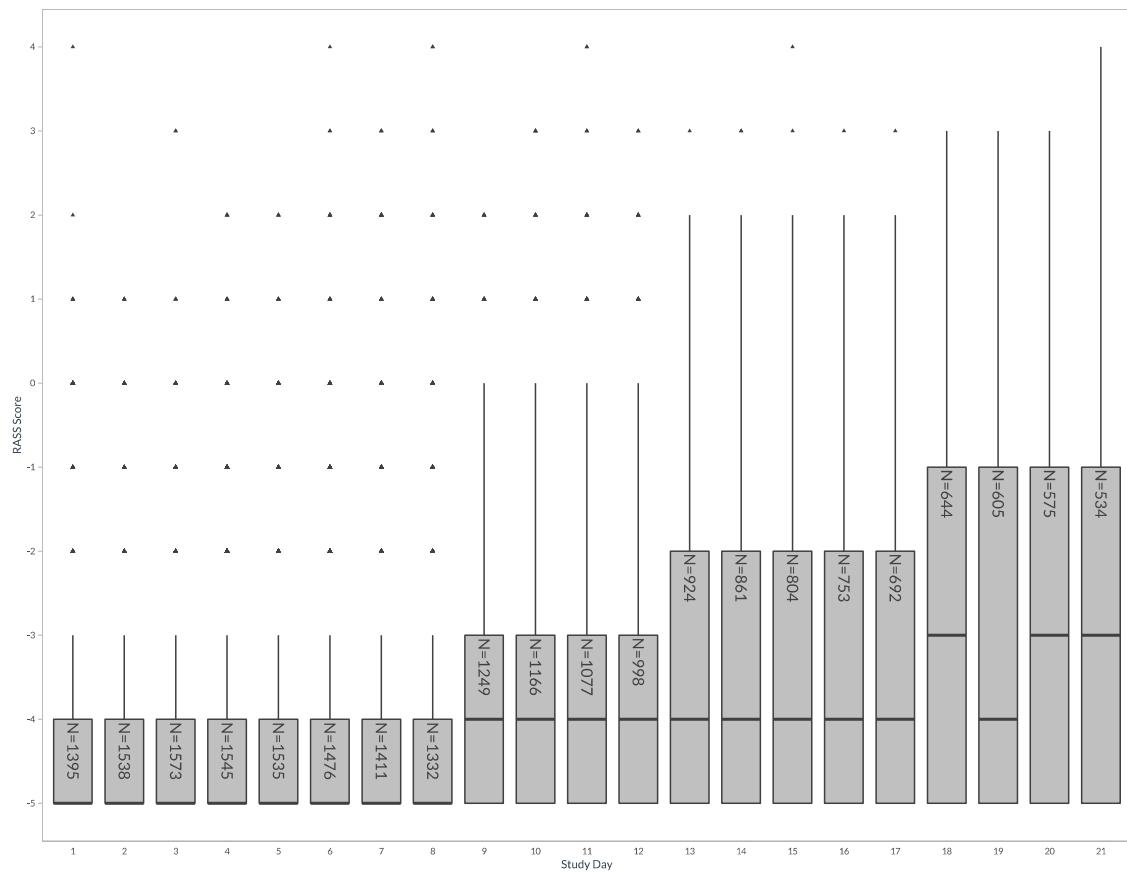
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Sites are listed in alphabetical order by country and city with lead country site and principal investigator (PI) listed first if there was one. Since Collaborators may have moved since working on the study, all personnel are listed at the site where they were when contributing to COVID-D.

Table S2: Eligible patients excluded by country

Country	Proportion of total number of patients enrolled N = 2088	Proportion of total number excluded because the site's capacity to collect data in the 2-week data collection period was exceeded N=1036
Spain	1150 (55.1%)	363 (35.0%)
United States of America	302 (14.5%)	525 (50.7%)
Italy	175 (8.4%)	105 (10.1%)
Netherlands	83 (4.0%)	0 (0.0%)
France	71 (3.4%)	36 (3.5%)
Turkey	64 (3.1%)	0 (0.0%)
Portugal	63 (3.0%)	3 (0.3%)
Belgium	48 (2.3%)	0 (0.0%)
Norway	44 (2.1%)	0 (0.0%)
Chile	43 (2.1%)	4 (0.4%)
Switzerland	25 (1.2%)	0 (0.0%)
Greece	7 (0.3%)	0 (0.0%)
Tunisia	10 (0.5%)	0 (0.0%)
Libya	3 (0.1%)	0 (0.0%)

Figure S1: Most sedated RASS score while on invasive mechanically ventilation over time



The boxplots show the median (dark horizontal line), interquartile range and outlier of most sedated RASS scores for patients on mechanical ventilation for each day. The N represents the number of patients on IMV each day. The outlier triangles can represent more than one patient.

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